REMARKS

Claims 7-32 are pending in this application, as previously shown. Claims 20-32 have been withdrawn from consideration pursuant to an election of species requirement.

SPECIFICATION/DRAWINGS

For the reasons of record, Applicants reiterate their position that FIG. 12 does not add new matter.

Applicants are extremely dismayed at the Examiner's willful misinterpretation of an obvious typographical error as an admission that Applicants have somehow "acknowledged" that Figure 12 added new matter. In fact, it is clear that the cited sentence of Applicants' previous response inadvertently omitted the word "not." Indeed, the sentence is grammatically improper as written. Only if the obvious missing word "not" is included, does this sentence make sense.

In any event, the objection has been obviated by inclusion of the sequences depicted in FIG. 12 in the body of the specification. As set forth in M.P.E.P. § 608.01(p), Applicants must be afforded the opportunity to amend their specification to include material incorporated by reference and deemed "essential." *See, also,* In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In sum, Applicants reiterate that **no** new matter has been added by the amendments herein, or by the previous submission of FIG. 12.

35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 7-29 were again rejected for a variety of reasons under 35 U.S.C. § 112, first paragraph as allegedly not described by the specification as filed. (Final Office Action, paragraphs 3 and 4). It was maintained that the recitation of fragments of 8 amino acids in length are not disclosed in the specification as filed. (Final Office Action, last paragraph on page 3). Applicants previous arguments have been deemed "unpersuasive" on the grounds that "the specification does not define the protein as being a 'protein or its fragments'; rather it addresses protein on its own and then continues that the invention is also drawn to fragments of said protein. Thus, the "fifth aspect," the DNA encoding protein, reads on DNA encoding full-length protein, but not on DNA encoding

any other polypeptides comprising certain fragments of the protein." (Final Office Action, last paragraph on page 4).

Because the Examiner has improperly taken various teachings out of their proper context, Applicants traverse the rejection.

Applicants are mystified at the Examiner's continued insistence that nucleotide sequences encoding polypeptide fragments of 8 amino acids are not disclosed in the specification as filed. The Examiner's attention is again directed to page 17, lines 10-19, where it is stated:

> A polypeptide or amino acid sequence "derived from" a designated nucleic acid sequence refers to a polypeptide having an amino acid sequence identical to that of a polypeptide encoded in the sequence, or a portion thereof, wherein the portions consists of at least 3-5 amino acids, and more preferably at least 8-10 amino acids, and even more preferably, at least 11-15 amino acids, or which is immunologically identifiable with a polypeptide encoded in the sequence. This terminology also includes a polypeptide expressed from a designated nucleic acid sequence.

Thus, not only does the specification clearly describe polypeptide fragments of 8-10 amino acids, it also clearly and unambiguously describes polynucleotide sequences encoding such fragments. Indeed, this is the point of the specification as a whole. Accordingly, withdrawal of this rejection is in order.

35 U.S.C. § 112, First Paragraph, Enablement

Claims 7-29 were also again rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification as filed. (Final Office Action, paragraph 5). In support of the rejection, the Examiner states, in part:

> The claims as amended are drawn to polynucleotides encoding polypeptides comprising specific immunogenic fragments of LT-A comprising at least eight residues and containing Arg in position corresponding to Ala-72. Prior art teaches that LT-A derivatives having Arg72 remained to be toxic. [citations omitted] The instant application demonstrates that full length LT-A has reduced toxicity as compared to wild-type, (Figs 4,5) but does not demonstrate any octamers of LT-A that are detoxified compared to wild type LT-A. Further, there is no description in the claims or specification sufficiently identifying epitope sequence. Consequently, there is no guidance on what fragments are required to maintain immunogenicity of the fragments required by the claims.

First and foremost, Applicants remind the Examiner that the claims are not solely directed to immunogenic fragments of LT-A. They are instead, directed to fragments that are both detoxified and immunogenic. With regard to the former (detoxification), Applicants have plainly identified in the specification, which residue(s) are essential for toxicity, namely residue Ala-72 of SEQ ID NOs:1 and 2; residue Ile-70 of SEQ ID NO:3 and residue Leu-70 of SEQ ID NO:4. Moreover, the critical residue involved in toxicity is recited in the claims, as all sequences must encode a fragment that includes the appropriate mutation at the appropriate residue to render the polypeptide detoxified.[1]

With regard to immunogenicity, Applicants remind the Examiner that the correlation between polypeptide structure (sequence) and immunogenic function is flexible. In other words, whereas essential residues are readily identifiable for enzymatic or toxic functions, any given polypeptide can tolerate multiple substitutions at various residues or deletions, while still retaining its immunogenic function. Thus, to the extent required, the correlation between structure and toxic/immunogenic functions is clearly laid out in the specification and claims.

Furthermore, it is not necessary for Applicants to present working examples of "immunogenic" detoxified fragments. It is more than ample that the specification as filed teaches one of skill in the art how to make and use the fragments as claimed. As noted above, the fragments must include a mutation at a specific residue, which renders the polypeptide detoxified. With regard to immunogenicity, the specification clearly teaches how test the detoxified polypeptide (or fragment) for the requisite immunogenic activity. Any fragment that includes the detoxifying mutation but which is not immunogenic remains outside the scope of the claims. Moreover, in order to satisfy the enablement requirement, Applicants need only show that the experimentation required to test immunogenicity is routine.[2] For the reasons of record, Applicants have met more than amply demonstrated that such testing is routine and, accordingly, the rejection is improper and should be withdrawn.

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[1] The references cited as allegedly establishing unpredictability remain entirely irrelevant inasmuch as the specification teaches that a mutation of the recited residue (Ala-72) to Arg would render the protein detoxified and, accordingly, any fragment including the specified mutation would be similarly detoxified.

[2] *See, also, United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989)), holding that routine experimentation, even if extensive (on the order of six or more months and tens of thousands of dollars), is not necessarily undue.

Simply put, the claimed fragments will be detoxified by virtue of the mutation at the specified residue, a finding set forth clearly in the specification as filed. Further, the immunogenic nature of any detoxified fragment can be readily tested and it is improper for the Office to require working examples to establish enablement.[3] Any "inoperative" embodiments are excluded from the scope of the claims and can be identified as such using routine experimentation.

Thus, the specification as filed more than amply satisfies the enablement requirement of Section 112, as one of skill in the art could make and use the claimed molecules without undue experimentation following the guidance set forth in the.

35 U.S.C. §§ 102/103

Claims 7-29 were also again rejected as allegedly unpatentable over EP 145486. (Final Office Action, paragraph 6). It is alleged that this reference discloses a modified LT-A protein including the octameric sequence TGFVRYDDG, where the R is at position 72 of this protein. In support of the rejection, the Examiner states, in part:

> The only meaning that Examiner reads into the limitation of fragment comprises "amino acid residue corresponding to Ala-72 of SEQ ID NO:1" is that the residue which is being replaced as claimed has to be a residue corresponding to Ala, i.e., it has to be any Ala replaced by any, in this case, Arg residue. Any Ala residue will be "corresponding" to any other Ala residue because they are the same by their nature.

As a threshold matter, Applicants remind the Office that it is contrary to basic fairness and public policy for the Office to reintroduce rejections that have been previously withdrawn (*see, e.g.*, M.P.E.P. § 706.07):

> To bring the prosecution to as speedy conclusion as possible and at the same time to deal justly by both the applicant and the public, the invention as disclosed and claimed should be thoroughly searched in the first action and the references fully applied; and in reply to this action the applicant should amend with a view to avoiding all the grounds of rejection and objection. Switching from one subject

[3] Applicants also note that the Examiner has not addressed references previously submitted (*e.g.*, Habeeb, Stylos), which references provide explicit evidence that analysis of peptide fragments for their immunogenicity was routine at the time of filing.

> matter to another in the claims presented by applicant in successive amendments, or from one set of references to another by the examiner in rejecting in successive actions claims of substantially the same subject matter, will alike tend to defeat attaining the goal of reaching a clearly defined issue for an early termination, i.e., either an allowance of the application or a final rejection.

In the pending case, Applicants addressed the rejection based on EP145486 in a response filed November 12, 2002. The rejection was not reiterated in the Office Action mailed on May 5, 2004 and was, therefore, considered withdrawn. It is improper for the Office to reintroduce rejections that have been overcome and, on this basis alone, withdrawal of the rejection is in order.

Nonetheless, for the sake of completeness, Applicants again address the rejection *per se*. For the reasons of record, Applicants reiterate that the Examiner is not entitled to read claim limitations in a vacuum. In particular, it is error to read the limitation regarding the residue corresponding to Ala-72 without considering the position (*e.g.*, residue 72) specified in the claim.

Therefore, when the claim is properly read as a whole, it is clear that not any alanine residue can be replaced with an arginine residue. Indeed, the claims not only require replacement of a residue "corresponding to" an alanine residue with an arginine residue, the claims (and specification) specify the particular position of the alanine that must be replaced, with respect to a reference sequence (SEQ ID NO:1). It is improper to ignore this explicit limitation of position of the alanine and assert that any toxic protein that includes any Ala-Arg substitution reads on the pending claims.

Accordingly, to fall within the scope of the claims, the fragment must include SLRSAHL**R** or **R**GQSILSG (where the bolded R indicates the replaced Ala at position 72. Such fragments are not disclosed in EP145486. In fact, in EP145486, the alanine residue corresponding to Ala-72 of SEQ ID NO:1 remains an alanine (see, residue 89 of the sequence cited in paragraph 6 of the Final Office Action). Thus, even if the rejection had not been previously withdrawn, it is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicant submits that the claims are now in condition for allowance and requests early notification to that effect. Please direct all further communications regarding this application to:

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Respectfully submitted,

Date: November 9, 2004

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